International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 10, October 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.10.2024.110

**ORIGINAL RESEARCH**

# Antimicrobial activity of ceftazidime-avibactam among carbapenem-resistant enterobactrales

[1]Dr. A.Shamili, [2]Dr. Arundhathi, [3]Dr. Deepalaksmi, [4]Dr. Sneha Kukanur.F, [5]Dr. Venkatesh.V.N

[1,3]Post graduate, [2,4]Assistant Professor, [5]Head of the Department, Department of Microbiology, Karwar Institute of Medical Sciences, India

**Corresponding author**
Dr. A.Shamili
Post graduate, Department of Microbiology, Karwar Institute of Medical Sciences, India
**Email:** shamilisham2597@gmail.com

Received Date: 23 August, 2024 Accepted Date: 25 September, 2024

## ABSTRACT

**Introduction:** The prudent utilization of antibiotics has resulted in the rise of multidrug resistance within Enterobacterales, mainly attributable to the production of beta-lactamases like Carbapenemases. Combination therapy, particularly Ceftazidime-Avibactam (CZA), has emerged as a preferred strategy. Resistance to this combination has also been noted, prompting this investigation to evaluate CZA's in vitro susceptibility against multidrug-resistant pathogens.

**Objectives:**

1. To isolate and identify CRE from various clinical samples
2. To assess CZA's in vitro susceptibility to these CRE isolates.

**Material & methods:** In the course of a six-month observational research, all samples obtained at the microbiology lab, were examined. Identification of Enterobacterales was carried out using standard techniques. CRE strains were identified by conventional Mcim and microbroth dilution methods through the Vitek-2 system. Testing for CZA in CRE strains was conducted using the Kirby Bauer disc diffusion method as well as MIC determination with the Vitek-2 system. **Results:** In a sample set of 45 specimens, 33% and 67%, respectively, of the detected CRE isolates were *Klebsiella pneumoniae&Escherichia coli*. Among the E. Coli isolates, 29% (13) exhibited susceptibility to CZA, while 38% (17) showed resistance to CZA. Regarding Klebsiella pneumoniae, 13% (6) were susceptible to CZA, whereas 20% (9) displayed resistance to CZA. **Conclusion:** The IDSA (Infectious Diseases Society of America) states that the CZA is a preferred single-drug therapy for curing infections caused by CRE. However, a rise of resistance to CZA is a growing concern, leading to the need for careful monitoring to improve its effectiveness.

**Keywords:** antimicrobial resistance, Ceftazidime-avibactum, infection control.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

## INTRODUCTION

Antimicrobial resistance (AMR)presents a significant risk to world well-being & health and affects people from different socioeconomic backgrounds. The WHOhas acknowledged AMR as “a global health security threat that requires action across government sectors and society as a whole”.(1)

The burden of AMR among the Gram-negative bacteria (GNB) presents a daily challenge for physicians working in intensive care units (ICUs). This burden highlights the consequences of bacteria acquiring drug resistance to multiple drugs, a phenomenon fueled by increasing selection pressure brought on by the overuse and misuse of antibiotics over time.(2,3).

The multifaceted nature of antimicrobial resistance in GNB encompasses both enzymatic as well as non-enzymatic mechanisms. Enzyme pathways entail the production of antibiotic-inactivating enzymes, which directly degrade or modify antibiotics, whereas non-enzymatic mechanisms involve alterations in bacterial cell structures or the enhancement of efflux pumps, diminishing antibiotic efficacy. This dual strategy of resistance underscores the adaptability of GNB and emphasizes the urgent necessity for innovative approaches to address this escalating global health threat.(4)

Resistance to antibiotic classes like cephalosporins, penicillins, and carbapenems is conferred by enzymatic inhibition via the production of different types of beta-lactamases, including ESBL (Extended-Spectrum Beta-Lactamases), MBL (Metallo-Beta-Lactamases), AmpC beta-lactamases, and



©2024 Int. J. Life Sci. Biotechnol. Pharma. Res.

DOI: 10.69605/ijlbpr_13.10.2024.110

carbapenemases. This makes the organism highly resistant to these important antibiotic therapies.(5)

The surge in antibiotic resistance has grave implications, leading to significant loss of life. More fatalities worldwide were directly caused by AMR in 2019 than by HIV and malaria combined, totaling 1.27 million. (6)

It is concerning to note that estimates suggest that by 2050, AMR will be mostly affecting Asia, with 4.7 million fatalities directly related to AMR.(7). Interestingly, India has one of the highest rates of AMR, underscoring the urgency for targeted interventions to mitigate this escalating health crisis.(8)

Ineffective infection prevention control (IPC) methods and easy access to drugs without a prescription are among the difficult aspects that add to the burden of AMR in India. Antimicrobial usage peaked in 2010 in India [9], with limited laboratory resources for disease-based diagnosis and inadequate, consistent, and effective surveillance systems to monitor drug-resistant trends and consumption (10)

The treatment available for MDR pathogen is limited and usage of monotherapy leads to the development of resistance.CZA is a novel cephalosporin that contains β-lactamase inhibitor and is not a beta-lactam. (11)

Avibactam inhibits ESBLs, AmpC β-lactamases (expressed in *Pseudomonas aeruginosa* and *Enterobacteriaceae*), OXA-48 β-lactamase family, and class A carbapenemases (such the *Klebsiella pneumoniae*carbapenemase KPC). CZA is used to treat severe cUTI (complicated Infections Of The Urinary Tract), cIAI (difficult Intra-Abdominal Infections), HAP (Hospital-Acquired Pneumonia) including VAP, & infections resulting from Gram-negative bacteria for which there are no viable treatment options. (12,13)

With all these above considerations the need for a combination of antimicrobial therapy is important to overcome the MDR pathogens. So in this study, we are going to evaluate CZA's in vitro susceptibility opposing MDR pathogens.

## MATERIAL & METHODS

A six-month cross-sectional study was conducted in the microbiology department of the Karwar Institute of Medical Sciences in Karwar, Karnataka, from February 2023 to July 2023, following approval from the ethics council.

All samples (pus, sputum, fluid, blood & body fluids, urine) received in the microbiology lab were included, where enterobactrales were identified as per the standard method.(14)

CRE isolates were identified by both conventional Mcim and microbroth dilution by the Vitek-2 system.

The procedure for Mcim involves incubating a meropenem disc (AST disc with a 10µg drug concentration) in a tryptic soy broth containing one µl loopful of the test organism for two hours. After two hours, the ATCC strain of *E. coli* is grown in a lawn culture. in accordance with the accepted disc diffusion testing procedure. After being removed from the broth, the meropenem disc is positioned on top of the lawn culture and incubated at 37°C for the entire night. The following day, the zone of inhibition of the meropenem disc is measured for diameter.(15)

The drug in the disc was active if the zone diameter was within the susceptible range, indicating that the test isolate was not producing carbapenemase. The test isolate's ability to produce carbapenemase is confirmed if the zone diameter is within the resistance range, indicating that the isolate's carbapenemase inactivated the meropenem in the disc.

The Vitak-2 system for MIC and the Kirby Bauer disc diffusion method for CZA were used to test the susceptibility of the CRE isolates. (15).The test isolate was cultured in a lawn culture for 24 hours at 37°C using 30/20 µg of ceftazidime-avibactum.The zone diameter was measured and assessed the next day. The same CRE isolate was analyzed in the VITEK 2 to determine the MIC of CZA using GN ID and 407 AST card (upper panel).

## RESULTS

Out of 645 samples received in 6 months, 297 were GNB,among them 143 were enterobactrales.Among these, 45 were CRE. The CRE isolated in our was E.coli(67%) & Klebsiella pneumoniae (33%) as shown in chart 1.Out of 45 CRE isolates, 19 (42%)were susceptible to CZA, and 26(58%) were resistant to CZA shown in chart 2. The susceptibility pattern of CZA among CRE isolates in various samplesis shown in chart 3.

CRE isolated were common in pus samples followed by urine and respiratory samples.



©2024 Int. J. Life Sci. Biotechnol. Pharma. Res.

DOI: 10.69605/ijlbpr_13.10.2024.110

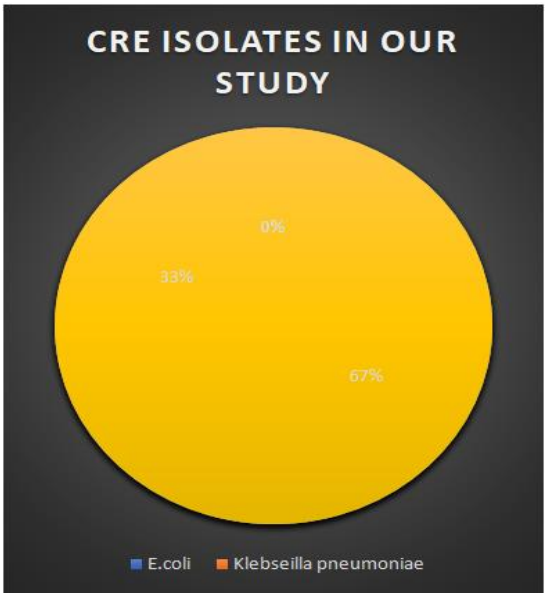


**CHART 1: CRE ISOLATES IN OUR STUDY**

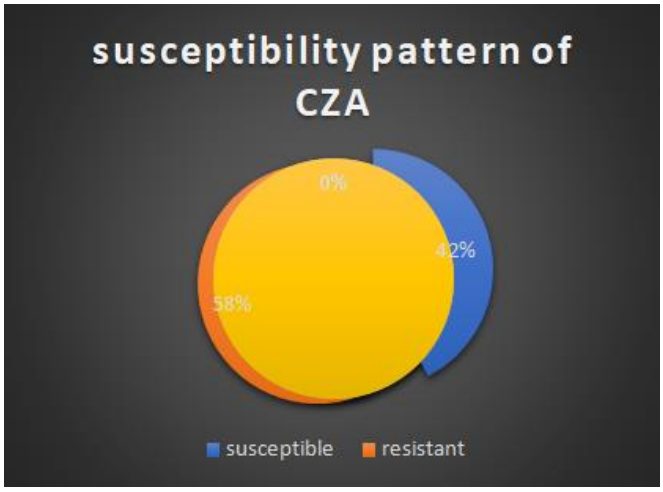


**CHART 2: SUSCEPTIBILITY PATTERN OF CZA AMONG CRE**

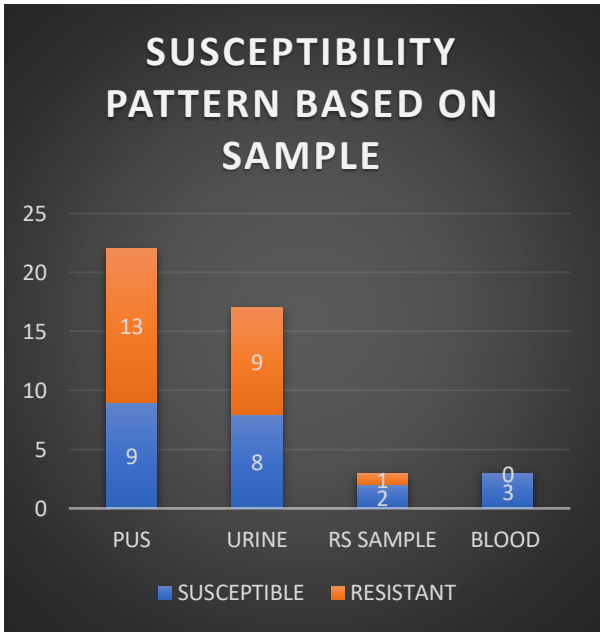


**CHART 3: SUSCEPTIBILITY PATTERN OF CZA AMONG CRE ISOLATES BASED ON SAMPLE**



©2024 Int. J. Life Sci. Biotechnol. Pharma. Res.

DOI: 10.69605/ijlbpr_13.10.2024.110

## DISCUSSION

For an early diagnosis and suitable treatment, carbapenem resistance must be identified as soon as possible.

Selecting an antibiotic therapy for gram-negative illnesses resistant to carbapenem is nearly always challenging. It is crucial for clinicians to comprehend the processes underlying resistance, whether they are caused by the synthesis of carbapenemase (NDM,VIM,IMP, KPC,OXA-23/24,OXA-48 alike), Alternatively by different mechanisms (loss of porin and carbapenem resistance due to efflux pump). [(16).]

The more well-known BL-BLI combination groups of antibiotics, such as ticarcillin-clavulanate, AMC, ampicillin-sulbactam, PTZ, CFS, etc., are almost ineffective against these CROs. The therapy options against these bugs have been strengthened with the introduction of a number of innovative BL-BLIs. These consist of imipenem-relebactam, ceftolozane-tazobactam, meropenem-vaborbactam, and ceftazidime-avibactam, the antibiotic under investigation in this work. [(17).]

It has been shown that CAZ-AVI resistance can develop in both in vitro and clinical settings. Before CAZ-AVI therapy was available, a patient with a KPC-producing K. pneumoniae (KPC-Kp) strain had never received CAZ-AVI therapy. This patient's case is the first known instance of CAZ-AVI resistance.[(18).]

According to our investigation, there were 45 total CRE isolatesofwhich 58% were susceptible to CZA.This is consistent with research by Diekema *et al.* [(19)]& Leal *et al.*[(20)] which concluded that *E. Coli* was the most frequently isolated pathogen. The CAZ-AVI sensitivity of these CRE is only 42%, as opposed to 45% in a few previous investigations. [(21).]

For the treatment of infections brought on by GNB for which there are few effective treatment options like CAUTI, IAIand VAP, CZA is advised. For persons with a creatinine clearance greater than 50, an intravenous dosage of 2 g every 8 hours is advised. [(22,23)]

However, one has to take measures to reduce the MDRO by following a different and useful approach and averting damage from MDRO infections is IPC (Infection Prevention & Control). This technique comprises two types of interventions: horizontal and vertical. Horizontal interventions use uniform techniques to reduce the spread of various diseases at the same time, while vertical therapies reduce specific infections by active screening programs followed by decontamination. [(24)]

IPC measures are advised by national and local recommendations to control MDRO transmission in LTCFs (Long-Term Care Facilities). [(25,26)]

## CONCLUSION

Two main antibiotics which are available for CRE are colistin, tigecycline but the antibiotics have serious side effects and higher mortality rates when compared to CZA medications that work against CRE isolates are a unique combination of βlactam/β-lactamase inhibitors.

According to the IDSA, CZA is a recommended therapeutic choice when administered as monotherapy for infections brought on by CRE. Constant interactions between microbiologists, clinicians, and infection control personnel for appropriate usage of antibiotics & improvement of infection control protocols to improve clinical outcomes and stop the emergence of AMR.

## ACKNOWLEDGEMENT

I express my sincere gratitude towards all the laboratory staff and faculty members of department of microbiology, Karwar institute of medical sciences, karwar for their support and help throughout the research work

**CONFLICT OF INTEREST**: none

## REFERENCES

1. Organization WH. Antimicrobial Resistance: Global Report on Surveillance. 2014; http://wwwwhoint/drugresistance/documents/surveillancereport/en/
2. Salam MA, Al-Amin MY, Salam MT, Pawar JS, Akhter N, Rabaan AA, Alqumber MA. Antimicrobial resistance: a growing serious threat for global public health. InHealthcare 2023 Jul 5 (Vol. 11, No. 13, p. 1946). MDPI.
3. Alekshun MN, Levy SB. Molecular mechanisms of antibacterial multidrug resistance. Cell. 2007 Mar 23;128(6):1037-50.
4. Barbier F, Andremont A, Wolff M, Bouadma L. Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management. Current opinion in pulmonary medicine. 2013 May 1;19(3):216-28.
5. S Apurba Deepashree R Sastry. Essentials Of Hospital Infection Control. S.L.: Jaypee Brothers Medical P; 2019.
6. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, Han C, Bisignano C, Rao P, Wool E, Johnson SC. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The lancet. 2022 Feb 12;399(10325):629-55.
7. Gopalkrishnan R, Walia K, Ohri V. Treatment guidelines for antimicrobial use in common syndromes.
8. Taneja N, Sharma M. Antimicrobial resistance in the environment: The Indian scenario. Indian Journal of Medical Research. 2019 Feb 1;149(2):119-28.
9. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, Laxminarayan R. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. The Lancet infectious diseases. 2014 Aug 1;14(8):742-50.
10. Aljeldah MM. Antimicrobial resistance and its spread is a global threat. Antibiotics. 2022 Aug 9;11(8):1082.
11. van Duin D, Bonomo RA. Ceftazidime/avibactam and ceftolozane/tazobactam: second-generation β-lactam/β-lactamase inhibitor combinations. Clinical Infectious Diseases. 2016 Jul 15;63(2):234-41.



©2024 Int. J. Life Sci. Biotechnol. Pharma. Res.

DOI: 10.69605/ijlbpr_13.10.2024.110

12. Shirley M. Ceftazidime-avibactam: a review in the treatment of serious gram-negative bacterial infections. Drugs. 2018 Apr;78:675-92.
13. Zhanel GG, Lawson CD, Adam H, Schweizer F, Zelenitsky S, Lagacé-Wiens PR, Denisuik A, Rubinstein E, Gin AS, Hoban DJ, Lynch JP. Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor combination. Drugs. 2013 Feb;73:159-77.
14. Mackie &mccartney.test for identification of bacteria :Jerald J, Andrew.G, barrie.P, Anthony.S. practical medical microbiology. 14th edition. Elsevier publishing 2011.p131-150.
15. CLSI. Performance standards for antimicrobial susceptibility testing M100, 33rd ed. ;2023.
16. Livermore DM, Nicolau DP, Hopkins KL, Meunier D. Carbapenem-Resistant Enterobacterales, Carbapenem Resistant Organisms, Carbapenemase-Producing Enterobacterales, and Carbapenemase-Producing Organisms: Terminology Past its "SellBy Date" in an Era of New Antibiotics and Regional Carbapenemase Epidemiology. Clin Infect Dis. 2020;71(7):1776-1782
17. Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-lactam–β-lactamase inhibitor combinations. Clinical microbiology reviews. 2020 Dec 16;34(1):10-128.
18. Humphries RM, Yang S, Hemarajata P, Ward KW, Hindler JA, Miller SA, Gregson A. First report of ceftazidime-avibactam resistance in a KPC-3-expressing Klebsiella pneumoniae isolate. Antimicrobial agents and chemotherapy. 2015 Oct;59(10):6605-7.
19. Leal HF, Azevedo J, Silva GE, Amorim AM, de Roma LR, Arraes AC, Gouveia EL, Reis MG, Mendes AV, de Oliveira Silva M, Barberino MG. Bloodstream infections caused by multidrug-resistant gram-negative bacteria: epidemiological, clinical and microbiological features. BMC infectious diseases. 2019 Dec;19:1-1.
20. Alatoom A, Elsayed H, Lawlor K, AbdelWareth L, El-Lababidi R, Cardona L, Mooty M, Bonilla MF, Nusair A, Mirza I. Comparison of antimicrobial activity between ceftolozane–tazobactam and ceftazidime–avibactam against multidrug-resistant isolates of Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa. International Journal of Infectious Diseases. 2017 Sep 1;62:39-43.
21. Diekema DJ, Hsueh PR, Mendes RE, Pfaller MA, Rolston KV, Sader HS, Jones RN. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrobial agents and chemotherapy. 2019 Jul;63(7):10-128.
22. Chen M, Zhang M, Huang P, Lin Q, Sun C, Zeng H, Deng Y. Novel β-lactam/β-lactamase inhibitors versus alternative antibiotics for the treatment of complicated intra-abdominal infection and complicated urinary tract infection: a meta-analysis of randomized controlled trials. Expert Rev Anti Infect Ther. 2018 Feb;16(2):111-120
23. Shiber S, Yahav D, Avni T, Leibovici L, Paul M. β-Lactam/β-lactamase inhibitors versus carbapenems for the treatment of sepsis: systematic review and meta-analysis of randomized controlled trials. Journal of Antimicrobial Chemotherapy. 2015 Jan 1;70(1):41-7.
24. Wong VW, Huang Y, Wei WI, Wong SY, Kwok KO. Approaches to multidrug-resistant organism prevention and control in long-term care facilities for older people: a systematic review and meta-analysis. Antimicrobial Resistance & Infection Control. 2022 Jan 15;11(1):7.
25. Eikelenboom-Boskamp A, Haaijman J, Bos M, Saris K, Poot E, Voss A, expert group 'Long-term care facilities' of the former Dutch Working Party on infection control Stobberingh E. Gorissen-Douven E. Molenaar P. Hoentjen R. Tolsma P. VerzijlI.. Dutch guideline for preventing nosocomial transmission of highly-resistant micro-organisms (HRMO) in long-term care facilities (LTCFs). Antimicrobial Resistance & Infection Control. 2019 Aug 27;8(1):146.
26. Wisconsin Healthcare-Associated Infections (HAI) Prevention Program . *Guidelines for prevention and control of antibiotic resistant organisms in health care settings.* Wisconsin: Wisconsin Division of Public Health, Bureau of Communicable Diseases; 2005



©2024 Int. J. Life Sci. Biotechnol. Pharma. Res.